Remarks

Reconsideration of this Application is respectfully requested.

Upon entry of the foregoing amendments, claims 1, 2, 4, 5, 10 and 16 are pending in the application, with claim 1 being the sole independent claim. Claims 5, 10 and 16 are sought to be amended, and claims 3, 6-9, 11-15 and 17-37 are sought to be cancelled without prejudice to or disclaimer of the subject matter encompassed thereby. These changes are believed to introduce no new matter, and their entry is respectfully requested.

Based on the above amendments and the following remarks, Applicants respectfully request that the Examiner reconsider all outstanding objections and rejections and that they be withdrawn.

I. Support for Amended Claims

Support for amended claim 5 can be found, inter alia, at page14, paragraph 22 through page 15 and in claim 5 as originally filed.

Support for the amended claim 10 can be found, inter alia, at page 15 and in claim 10 as originally filed.

Support for amended claim 16 can be found, inter alia, at page14, paragraph 21 and in claim 16 as originally filed.

II. Summary of the Office Action

In the Office Action dated November 7, 2003, the Examiner has made one objection to, and nine rejections of, the claims. Applicants respectfully offer the following remarks concerning each of these elements of the Office Action.

III. Objection to Claim 16

At page 2, paragraph 5 of the Office Action, the Examiner objects to claim 16 because it depends from non-elected claim 11. By the foregoing amendments, Applicants have amended claim 16 such that this claim no longer depends from claim 11. Therefore, Applicants respectfully request that the objection be reconsidered and withdrawn.

IV. Rejections under 35 U.S.C. § 112, first paragraph

A. Enablement

At pages 3-7, paragraph 8 of the Office Action, the Examiner rejects claims 1-2, 4-5, 10 and 16 under 35 U.S.C. § 112, first paragraph for lack of enablement. The Examiner states that it would require undue experimentation by one skilled in the art to practice the claimed invention. Applicants respectfully traverse the rejection.

1. Examiner's Burden

The Examiner bears the initial burden of proving that a specification is non-enabling. *See In re Marzocchi*, 169 USPQ 367 (C.C.P.A. 1971). A specification is presumed to be enabling unless the Examiner provides acceptable objective evidence or sound scientific reasoning showing that it would require undue experimentation for one of ordinary skill in the art to make and use the claimed invention. *See Id.*; *see*

also In re Wright, 999 F.2d 1557, 1562 (Fed. Cir. 1993). In the present case, the Examiner's burden has not been satisfied.

In making this rejection, the Examiner first contends that the specification does not sufficiently enable the method of modulating the immune system of any animal by contacting any antigen-presenting cell with an effective amount of any retinoid and any cytokine for treating any disease. Applicants respectfully assert that the Examiner's use of the phrase "for treating *any* disease" is a mischaracterization of the invention. The specification states that the invention may be used to treat ". . . a physical disorder that may be delayed, prevented, cured or otherwise treated by differentially modulating immune system function . . . ." (*see* Specification at page 22). Therefore, the Examiner's use of the word "any" in this context is inappropriate, as Applicants are not claiming the treatment of *any* disease. Additionally, as will be discussed in detail in section (IV)(A)(4), *infra*, any retinoid, cytokine and antigen-presenting cell can be routinely tested, by any of a number of assays disclosed in the specification, to determine their usefulness in the method of the invention. (*see* Specification at pages 58-72). Applicants submit that the full scope of the claimed methods and compositions could be practiced and made by those of ordinary skill in the art without undue experimentation. Additionally, Applicants assert that the Examiner has not provided a sufficient explanation or sound scientific reasoning as to why the specification would not enable the claimed invention; therefore, the Examiner has not established a *prima facie* case of non-enablement.

2. What is Known in the Art

At page 5 of the Office Action, the Examiner states that the specification does not teach how to make any pan-RXR agonist, any RAR antagonist, any Compound V, any Compound II, any Compound VIII and or any ester or prodrug thereof. The Examiner goes on to state that the specification also fails to teach how to make any analog or derivatives of tumor necrosis factor α (TNFα) or interleukin-1β (IL-1β) for the claimed method of modulating the immune system of an animal. Applicants respectfully disagree with these contentions.

In order to enable a claimed invention, a specification need not teach, and preferably omits, information that is well-known to those of ordinary skill in the art. *See Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1384 (Fed. Cir. 1986); *Lindemann Maschinenfabrik v. American Hoist and Derrick*, 730 F.2d 1452, 1463 (Fed. Cir. 1984); *In re Wands*, 8 USPQ2d 1400, 1402 (Fed. Cir. 1988). In addition, one of ordinary skill in the art is deemed to know not only what is considered well-known, but also where to search for any needed starting materials. *See In re Howarth*, 210 USPQ 689, 692, (CCPA 1981). Under these standards, the present specification fully enables the presently claimed invention.

Pages 38-58 of the specification disclose not only a number of RXR and RAR agonists and antagonists, but also the sources from which information about these compounds can obtained. Specifically, the specification discloses sources where the structures and/or methods of synthesis can be found for Compounds I, II, III, IV, V, VI, VII, VIII and SR11237 (*see* Specification, *e.g.*, page 57, paragraph 103 and page 58, Table 1b). The specification also discloses a general method for synthesizing

Compound III (*see* Specification page 54, paragraph 100, through page 55, paragraph 101).

The specification goes on to disclose a number ways in which cytokines, both natural and synthetic, can be procured. These include isolation from natural sources such as activated monocytes or macrophages, production using recombinant DNA techniques familiar to the ordinarily skilled artisan, acquisition from commercial sources and synthesis according to standard methods of protein synthesis. Both nucleotide sequences and three-dimensional protein structures for cytokines are well known in the art. With this knowledge, fully active variants, analogues and derivatives of cytokines can be produced and used in the method of the invention, and need not be taught by the specification in order to enable the claimed invention (*see* Specification pages 72-73, paragraph 137).

Additionally, at page 6 of the Office Action, the Examiner states that given the indefinite number of undisclosed pan-RXR agonists, RAR antagonists, the diverse functions of each agonist, antagonist, analog and derivatives of TNFα and IL-1β through distinct receptor pathways, it is unpredictable which one of the undisclosed pan-RXR agonists, RAR antagonists, TNFα and IL-1β analogs and derivatives thereof would maintain the same structure and function and would be useful for modulating the immune system for treating any disease. To support this contention, the Examiner cites Stryer *et al.*, Ngo *et al.*, Attwood, Skolnick *et al.* and Geissmann *et al.* for the proposition that any changes to a protein, such as those found in a derivative or analogue, make the function of that protein unpredictable. Applicants respectfully disagree with these contentions.

The Examiner's attention is directed to pages 38-58 of the specification, which describe a large number of retinoids, including RAR agonists (selective for α, β and/or γ RARs, or pan RAR agonists), RXR agonists and RAR antagonists. For each of these groups both general structures and specific examples are disclosed (*see, e.g.* Specification at page 40). Moreover, the present specification provides detailed disclosure of assays useful in determining the function of a given retinoid analogue (*see, e.g.* Specification at pages 32, 34-35, 36, 58-70, and throughout the Examples). Hence, the present specification is replete with information relating to the structure and function of retinoids suitable for use in the claimed invention.

Therefore, in view of the teachings of the present specification and information that is known in the art (which, under *Hybritech*, *Lindemann Maschinenfabrik*, *Wands*, and *Howarth*, need not be taught in, and preferably is omitted from, the present specification), one of ordinary skill would be able to make and use retinoids, cytokines and antigen-presenting cells as claimed in claims 1-2, 4-5, 10 and 16 with a reasonable expectation of success and without undue experimentation. Hence, the present specification fully enables claims 1-2, 4-5, 10 and 16 as currently presented.

3. Need for Working Examples

At page 6 of the Office Action, the Examiner contends that "even if the claimed method is limited to [] specific retinoids . . . there is no in vivo working example demonstrating that the claimed method is effective for modulating the immune system for treating any disease." Applicants respectfully assert that this contention is irrelevant to the level of enablement provided by the present specification. In order to enable a claimed invention, a specification need not

disclose working examples. "Nothing more than objective enablement is required, and therefore it is irrelevant whether this teaching is provided through broad terminology or illustrative examples." *In re Wright*, 27 USPQ2d 1510, 1561 (Fed. Cir. 1999); *see also In re Borkowski*, 422 F.2d 904, 908 (C.C.P.A. 1970). Hence, whether or not the present specification provides working examples (or indeed, *any* examples) is not germane to the enablement of the claimed invention.

The Examiner admits, at page 3 of the Office Action, that the specification discloses a method for inhibiting retinol-induced apoptosis of Langerhans cells, as well as a method of enhancing antigen presentation in Langerhans cells. This disclosure, along with the disclosure of routine methods of testing (*see* Specification at pages 58-72) to determine the effects of various retinoids, cytokines and antigen-presenting cells in the method of the invention, fully enable claims 1-2, 4-5, 10 and 16 as currently presented.

If, instead, the Examiner is contending that the *in vitro* results presented in the specification are insufficient to enable *in vivo* methods, Applicants respectfully disagree. There is no requirement for clinical or *in vivo* data to prove that an application is in compliance with 35 U.S.C. § 112, first paragraph. In fact, the description of *in vitro* and/or animal testing has been held to enable claims to *in vivo* therapeutic compositions and methods of their use. To this end, the Federal Circuit has stated that:

> In vitro testing, in general, is relatively less complex, less time consuming, and less expensive than in vivo testing. Moreover, in vitro results with respect to the particular pharmacological activity are generally predictive of in vivo results, i.e., there is a reasonable correlation therebetween. Were this not so, the testing procedures of the pharmaceutical industry would not be as they are.

Cross v. Iizuka, 753 F.2d 1040, 1050 (Fed. Cir. 1985).

The present specification clearly describes methods for preparation and use of the claimed invention *in vitro* (*see e.g.*, Specification at pages 87-90). Under *Cross*, one of ordinary skill would thus recognize that the *in vitro* testing described in the present specification would be "generally predictive of *in vivo* test results," *Cross*, 753 F.2d at 1050, and thus would have a reasonable expectation that the claimed methods would be successful for the claimed *in vivo* methods. Thus, any contention to the contrary is legally and factually erroneous.

4. Undue Experimentation under Wands

Finally, at page 6, paragraph 6 of the Office Action, the Examiner concludes with the broad generalization that "it would require undue experimentation of [*sic*] one of ordinary skill in the art to practice the claimed invention." Applicants respectfully disagree with this contention.

As an initial matter, Applicants question the Examiner's reliance upon footnote 7 in *Ex Parte Aggarwal*, 23 USPQ2d, 1334, 1338 (BPAI 1992) (*see* Office Action at page 6, sixth paragraph). First, the text of this footnote is mere dicta, and does not form a basis for any holding by the Board. Moreover, the statements in this footnote relate to inactivation of a potential therapeutic *protein* via such mechanisms as proteolytic degradation, immunological activation and the like. Hence, the Board's conclusion in *Aggarwal* was based on the identity of the claimed compound as a *protein*. In contrast, the retinoids used in the presently claimed methods would not be expected to be subject to the same problems as the protein at issue in *Aggarwal*. Finally, the rejection at issue in *Aggarwal* was for lack of utility

under 35 U.S.C. § 101, *not* for lack of enablement under 35 U.S.C. § 112. As the MPEP states, the enablement requirement under 35 U.S.C. § 112, first paragraph, "is different from the utility requirement of 35 U.S.C. 101." MPEP § 2164.07 (February 2003). Hence, the Examiner's reliance on the footnote in *Aggarwal* is factually and legally unfounded.

It is requested that in reconsidering this rejection, the Examiner also keep in mind that the question of undue experimentation is a matter of degree, and "the key word is 'undue,' not 'experimentation.'" *In re Wands*, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988), quoting *In re Angstadt*, 190 USPQ 214, 219 (C.C.P.A. 1976). The fact that some experimentation is necessary does not preclude enablement; what is required is that the amount of experimentation not be unduly extensive. *PPG Indus., Inc. v. Guardian Indus. Corp.*, 37 USPQ2d 1618, 1623 (Fed. Cir. 1996), citing *Atlas Powder Co. v. E.I. DuPont De Nemours & Co.*, 224 USPQ 409, 413 (Fed. Cir. 1984). Furthermore, the test of whether an amount of experimentation is undue is not merely quantitative; a considerable amount of experimentation is permissible, if it is merely routine (*i.e.*, uses methods known to those of ordinary skill in the relevant arts), or if the specification provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed to enable the determination of how to practice a desired embodiment of the claimed invention. *See PPG Indus.*, 37 USPQ2d at 1623, citing *Ex parte Jackson*, 217 USPQ 804, 807 (Bd. Pat. App. & Inter. 1982).

As noted above, pages 58-72 of the specification disclose a number of methods to screen candidate compounds for their usefulness in the claimed invention. For example, the specification discloses a screening method in which a first antigen-

presenting cell is treated with candidate compounds, while a second antigen-presenting cell is left untreated, but incubated under identical conditions, to determine the abilities of the compounds to activate or induce/delay/prevent apoptosis in the treated cell. (*see* page 61, paragraph 119). Therefore, the functionality of a particular retinoid, and/or cytokine in modulating the immune system can be routinely tested by one skilled in the art in any number of assays disclosed in the specification without undue experimentation. Consequently, the present specification fully enables claims 1-2, 4-5, 10 and 16 as currently presented.

B. Written Description

At page 7, paragraph 9 of the Office Action, the Examiner rejects claims 1-2, 4-5, 10 and 16 under 35 U.S.C. § 112, first paragraph for lack of written description. The Examiner states that the rejected claims contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor had possession of the claimed invention. The Examiner's reasoning for the written description rejection is essentially the same as the reasoning for the enablement rejection as discussed above. Applicants respectfully traverse the rejection.

Applicants wish to remind the Examiner that "[a]dequate description under the first paragraph of 35 U.S.C. 112 does not require *literal* support for the claimed invention." "[T]he observation of a lack of literal support does not, in and of itself, establish a *prima facie* case for lack of adequate descriptive support under the first paragraph of 35 U.S.C. 112." *Ex parte Parks*, 30 USPQ2d 1234, 1236 (Bd. Pat. App. Int. 1994). Instead, the written description requirement of 35 U.S.C. § 112, first

paragraph, is met "if the originally-filed disclosure would have conveyed to one having ordinary skill in the art that an [applicant] had possession of the concept of what is claimed," *id.*, *i.e.*, "[i]f a person of ordinary skill in the art would have understood the inventor to have been in possession of the claimed invention at the time of filing, even if every nuance of the claims is not explicitly described in the specification . . . ." *In re Alton*, 37 USPQ2d 1578, 1584 (Fed. Cir. 1996). An applicant is not required to disclose or provide a working example of every species of a given genus in order to meet the written description requirement of 35 U.S.C. § 112 (*see Parks and Alton*), and subject matter that "might fairly be deduced from the original application" is considered to be described in the application as filed. *Acme Highway Prod. Corp. v. D.S. Brown Co.*, 431 F.2d 1074, 1080 (6th Cir. 1970) (citations omitted), *cert. denied*, 401 U.S. 956 (1971), *followed by Westphal v. Fawzi*, 666 F.2d 575, 577 (C.C.P.A. 1981). Moreover, "[a] description of a genus . . . may be achieved by means of recitation of a representative number of [species] . . . falling within the scope of the genus . . . ." *Regents of Univ. of Calif. v. Eli Lilly & Co.*, 119 F.3d 1559, 1569 (Fed. Cir. 1997).

As detailed above, the present specification describes the structures of a large number of retinoids, including RAR agonists (selective for α, β and/or γ RARs, or pan RAR agonists), RXR agonists and RAR antagonists. Citations for descriptions and/or methods of synthesizing these agonists and antagonists are also disclosed. Additionally, the specification discloses a number of methods to screen candidate retinoid and cytokine compounds and antigen-presenting cells for their usefulness in the presently claimed methods. As detailed above, because both nucleotide sequences and three-dimensional protein structures for cytokines are well known in the art,

sufficient written description exists in the specification such that fully active variants, analogues and derivatives of cytokines can be produced and used in the method of the invention. Finally, the specification discloses a method for inhibiting retinol-induced apoptosis of Langerhans cells, as well as a method of enhancing antigen presentation in Langerhans cells. Hence, under the standards set forth in *Parks*, *Alton*, *Acme* and *Eli Lilly*, the present specification provides sufficient written description to convey to one of ordinary skill that Applicants had possession of the full scope of the invention as claimed in claims 1-2, 4-5, 10 and 16.

C. Summary

Therefore, Applicants respectfully assert that the present specification is sufficiently enabling such that one of ordinary skill would be able to make and use the invention with a reasonable expectation of success and without undue experimentation. Additionally, the specification provides sufficient written description to convey to one of ordinary skill that Applicants had possession of the full scope of the claimed invention upon filing of the application. In view of the foregoing remarks, Applicants respectfully request that the rejections under 35 U.S.C. § 112, first paragraph be reconsidered and withdrawn.

V. Rejection under 35 U.S.C. § 112, second paragraph

At page 9, paragraph 11 of the Office Action, the Examiner rejects claims 5 and 10 under 35 U.S.C. § 112, second paragraph, as being indefinite. The Examiner states that the "salts, esters and prodrugs thereof" language in claim 5 is indefinite and ambiguous because "SR11237 is a singular compound," and suggests that the claim be amended to recite "salt, ester and prodrug thereof." The Examiner also states that the

"active fragments, variants, analogues and derivatives thereof" language in claim 10 is indefinite and ambiguous because TNFα and IL-1β as written is a singular compound. Applicants respectfully traverse the rejection.

By the foregoing amendments, Applicants have amended claim 5 to recite "any pharmaceutically acceptable salt, ester and prodrug thereof." Additionally, claim 10 has been amended to recite "any active fragment, variant, analogue and derivative thereof." Therefore, the Examiner's rejections has been fully accommodated, and reconsideration and withdrawal of the rejections are respectfully requested.

VI. Rejections under 35 U.S.C. § 102

A. Trinchieri et al.

At page 10, paragraph 13 of the Office Action, the Examiner rejects claims 1 and 10 under 35 U.S.C. § 102(b) as being anticipated by Trinchieri *et al.* The Examiner states that Trinchieri *et al.* teach a method of modulating the immune system of an animal by affecting the physiology of undifferentiated promyelocytic HL-60 cells with a retinoid and a cytokine. Applicants respectfully traverse the rejection.

Under 35 U.S.C. § 102, a claim can only be anticipated if every element in the claim is expressly or inherently disclosed in a single prior art reference. *See Kalman v. Kimberly Clark Corp.*, 713 F.2d 760, 771 (Fed. Cir. 1983), *cert. denied*, 465 U.S. 1026 (1984). This requirement is not met by the disclosure of Trinchieri *et al.*

Claim 1 recites "a method of modulating the immune system of an animal by affecting the physiology of an antigen-presenting cell in said animal, comprising contacting said antigen-presenting cell with an effective amount of at least one

retinoid and an effective amount of at least one cytokine, under conditions whereby the physiology of said antigen-presenting cell is affected." Trinchieri *et al.* studied the growth and differentiation of HL-60 cells using retinoic acid and tumor necrosis factor. HL-60 cells are a human myeloid cell line (*See* Trinchieri *et al.* p. 1218). These are undifferentiated promyelocytic cells that do not possess antigen-presenting capabilities. Moreover, Trinchieri *et al.* do not disclose acquisition of antigen-presenting capabilities by differentiated HL-60 cells. Indeed, even the initial report of the establishment and characterization of the HL-60 cell line provided no such information (*see* Gallagher *et al. Blood. 54*(3):713-733 (1979), cited as Doc. No. AT 75 in the Supplemental Information Disclosure Statement filed concurrently herewith). Despite conducting functional studies to characterize this cell line, Gallagher *et al.* do not disclose an ability of HL-60 cells to present antigen. The Examiner also has provided no objective information that HL-60 cells are antigen-presenting cells. Hence, the "antigen-presenting cell" limitation of claim 1 is not met. Therefore, Trinchieri *et al.* does not anticipate claim 1.

Furthermore, because claim 10 depends from claim 1, Trinchieri *et al.* cannot anticipate claim 10. As a rule, a dependent claim is "construed to incorporate by reference all the limitations of the claim to which it refers." 35 U.S.C. § 112, paragraph 4 (BNA 2001); *see also Bloom Eng'g Co. v. North Am. Mfg. Co.*, 129 F.3d 1247, 1250, 44 USPQ2d 1859, 1861 (Fed. Cir. 1997). Hence, because the "antigen-presenting cell" limitation is not met in claim 1, it is also necessarily not met in claim 10.

In view of the foregoing remarks, reconsideration and withdrawal of the rejection under 35 U.S.C. § 102(b) over Trinchieri *et al.* is respectfully requested.

B. Mehta et al.

At page 10, paragraph 14 of the Office Action, the Examiner rejects claims 1 and 2 under 35 U.S.C. § 102(b) as being anticipated by Mehta *et al.* The Examiner states that Mehta *et al.* teach a method of modulating the immune system by affecting the physiology of an antigen-presenting cell by contacting the cell with a retinoid such as all-trans retinoic acid and a cytokine such an interferon gamma (IFN-γ). Applicants respectfully traverse the rejection.

Applicants respectfully assert that Mehta *et al.* do not disclose each and every element of claim 1. The preamble of claim 1 recites "a method of modulating the immune system of an animal by affecting the physiology of an antigen-presenting cell in said animal." A preamble is limiting when it is necessary to give life, meaning and vitality to a claim. *Griffin v. Bertina*, 62 USPQ2d 1431, 1434 (Fed. Cir. 2002). If in the absence of the preamble's stated objective, subsequent claim language is without purpose or meaning, the preamble is limiting. *Id.* The preamble of claim 1 gives purpose to the recited method, *i.e.* provides a rationale and purpose for the method. Without the preamble, "contacting said antigen-presenting cells with an effective amount of least one retinoid and an effective amount of at least one cytokine" is empty language without function. Hence, the preamble of claim 1 is considered an element of this claim. To anticipate claim 1, Mehta *et al.* must, therefore, disclose methods of modulating the immune system *of an animal* by affecting the physiology of an antigen-presenting cell *in an animal.*

Mehta *et al.* do not disclose the modulation of the immune system of an animal by affecting the physiology of an antigen-presenting cell in an animal. The work by Mehta *et al.* was done with macrophages *in vitro*, and the reference does not

disclose the modulation of the immune system of an animal. Because the preamble of claim 1 is an element of this claim, and Mehta *et al.* do not disclose this element, Mehta *et al.* cannot anticipate claim 1.

Furthermore, because claim 2 depends from claim 1, Mehta *et al.* cannot anticipate claim 2. As a rule, a dependent claim is construed to incorporate by reference all the elements of the claim to which it refers. Hence, because all of the elements recited in the preamble of claim 1 are not met by the disclosure of Mehta *et al.*, these same elements in claim 2 are also not met by the disclosure of Mehta *et al.*

In view of the foregoing remarks, Applicants respectfully request that the rejection under 35 U.S.C. § 102(b) over Mehta *et al.* be reconsidered and withdrawn.

VII. Rejections under 35 U.S.C. § 103

A. Mehta et al. and Zhou et. al.

At page 11, paragraph 17 of the Office Action, the Examiner rejects claims 1 and 10 under 35 U.S.C. § 103(a) as being unpatentable over Mehta *et al.* in view of Zhou *et al.* The Examiner states that the invention of claim 10 differs from the teaching of Mehta *et al.* only in that the cytokine is TNFα. The Examiner states that Zhou *et al.* teach that cytokine treatment such GM-CSF, IL-4 and TNF induce monocyte-derived dendritic cell differentiation and increases antigen presentation to T cells. The Examiner concludes that it would have been obvious to one of ordinary skill in the art to substitute IFN-γ in the method taught by Mehta *et al.* for the various cytokines taught by Zhou *et al.* Applicants respectfully traverse the rejection.

In proceedings before the Patent and Trademark Office, the examiner bears the burden of establishing a *prima facie* case of obviousness based upon the prior art. *See*

In re Piasecki, 223 USPQ 785, 787-88 (Fed. Cir. 1984). The Examiner can satisfy this burden only by showing some objective teaching in the prior art or that knowledge generally available to one of ordinary skill in the art would lead that individual to combine the relevant teachings of the references in such a way as to produce the invention as claimed. *See In re Fine*, 5 USPQ2d 1596,1598 (Fed. Cir. 1988). What is needed is a reason, suggestion, or motivation in the prior art that would motivate one of ordinary skill to combine the cited references, and that would also suggest a reasonable likelihood of success in making or using the claimed invention as a result of that combination. *See In re Dow Chem. Co.*, 837 F.2d 469, 473 (Fed. Cir. 1988). Absent such suggestion and motivation, the cited references may not be properly combined to render the claimed invention obvious. *See In re Fine*, 5 USPQ2d 1596,1598 (Fed. Cir. 1988). In the present case, the Examiner's burden has not been satisfied.

In addition to the failure of Mehta *et al.* to disclose a key element of claim 1 (detailed above), there is no suggestion or motivation to combine Mehta *et al.* and Zhou *et al.* Thus, the Examiner has not met the burden required to establish a *prima facie* case of obviousness. Even if one skilled in the art were to combine Mehta *et al.* and Zhou *et al.*, this would not teach or suggest the invention of claims 1 and 10. As detailed above, Mehta *et al.* fail to disclose the element recited in the preamble of claim 1. Zhou *et al.* does not cure this defect in Mehta *et al.* Therefore the element in the preamble of claim 1, namely a method of modulating the immune system of an animal by affecting the physiology of an antigen-presenting cell in said animal, is not taught or suggested by the combination of Mehta *et al.* and Zhou *et al.* Because claim 10 depends from claim 1 and incorporates all of the limitations of claim 1, the

combination of Mehta *et al.* and Zhou *et al.* does not teach or suggest the invention of claim 10.

In making this §103(a) rejection, it appears that the Examiner has used hindsight reconstruction to pick and choose among unrelated and isolated disclosures to make the claimed invention appear obvious. As the Federal Circuit has held numerous times, a hindsight analysis such as that employed by the Examiner in the present case is impermissible -- instead, the Examiner must show suggestions, explicit or otherwise, that would compel one of ordinary skill to combine the cited references in order to make and use the claimed invention. *See, e.g., Interconnect Planning Corp. v. Feil*, 774 F.2d 1132, 1143 (Fed. Cir. 1985). The Board has also provided the same mandate on this issue:

> it is impermissible to use the claimed invention as an instruction manual or "template" to piece together isolated disclosures and teachings of the prior art so that the claimed invention may be rendered obvious . . . . a rejection based on § 103 must rest on a factual basis, with the facts being interpreted without hindsight reconstruction of the invention from the prior art. In making this evaluation, the examiner has the initial duty of supplying the factual basis for the rejection he advances. He may not, because he doubts that the invention is patentable, resort to speculation, unfounded assumptions or hindsight reconstruction to supply deficiencies in the factual basis.

Ex parte Haymond, 41 USPQ2d 1217, 1220 (Bd. Pat. App. Int. 1996).

In this § 103 rejection, the Examiner restates the purported teachings of individual pieces of art, and uses this as motivation to combine these individual pieces of art in an attempt to produce the claimed invention. This does not comport with the Federal Circuit's mandate that the Examiner show suggestions, explicit or otherwise, that would compel one of ordinary skill to combine the cited references in order to

make and use the claimed invention. Thus, the Examiner's hindsight analysis is impermissible and cannot be used to establish a *prima facie* case of obviousness.

Applicants have established above that Mehta *et al.* and Zhou *et al.* fail to teach all of the elements of Applicants' claims. Therefore, it follows that a combination of the reference teachings would *not* lead one of ordinary skill in the art to Applicants' claimed invention. Applicants respectfully remind the Examiner that the requisite motivation for establishing a *prima facie* case of obviousness *must* be found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. *See In re Kotzhab*, 217 F.3d 1365, 55 USPQ2d 1313 (Fed. Cir. 2000). Applicants contend that neither of the references provide a suggestion or motivation to modify the cited references or to combine reference teachings, nor is this motivation supplied by knowledge generally available to one or ordinary skill in the art. Therefore, the Examiner has not met the burden required to establish a *prima facie* case of obviousness.

In view of the foregoing remarks, Applicants respectfully request that the rejection under 35 U.S.C. § 103(a) over Mehta *et al.* and Zhou *et al.* be reconsidered and withdrawn.

B. Mehta et al. and U.S. Pat. No. 5,552,271

At page 12, paragraph 18 of the Office Action, the Examiner rejects claims 1-2 and 4-5 under 35 U.S.C. § 103(a) as being unpatentable over Mehta *et al.* in view of U.S. Patent No. 5,552,271 ("the '271 patent) to Pfahl *et al.* The Examiner states that the invention of claim 4 differs from the teaching of Mehta *et al.* only in the method wherein the retinoid is a pan-RXR agonist and an RAR antagonist. The Examiner

also states that the invention of claim 5 differs from Mehta *et al.* only in the method wherein a pan-RXR agonist is SR11237 and pharmaceutically acceptable salts, esters and prodrugs thereof. The Examiner states that the '271 patent teaches a method of inhibiting retinoid X receptor heterodimer formation using a pan-RXR agonist such as SR11237, and that it would have been obvious to one of ordinary skill in the art to substitute the retinoid as taught by Mehta *et al.* for the various retinoids as taught by the '271 patent. Applicants respectfully traverse the rejection.

There is no reason, suggestion, or motivation in the art that would compel one of ordinary skill to combine Mehta *et al.* and the '271 patent, and that would also suggest a reasonable likelihood of success in making or using the claimed invention as a result of that combination. Even if one skilled in the art were to combine Mehta *et al.* and the '271 patent, this would not teach or suggest the invention of claims 1-2 and 4-5. As detailed above, Mehta *et al.* do not disclose a key element of claim 1. The '271 patent does not cure this defect in Mehta *et al.* Mehta *et al.* and the '271 patent fail to teach all of the elements of Applicants' claims. Therefore, it follows that a combination of the reference teachings would *not* lead one of ordinary skill in the art to Applicants' claimed invention. The Examiner has again used impermissible hindsight reconstruction to combine two unrelated pieces of art in an attempt to render the claimed invention obvious. Therefore, the Examiner has not met the burden required to establish a *prima facie* case of obviousness.

In view of the foregoing remarks, Applicants respectfully request that the rejection under 35 U.S.C. § 103(a) over Mehta *et al.* and the '271 patent be reconsidered and withdrawn.

C. Dunlop et al. and Zhou et al., or Hausser et al. or Cumberbatch et al.

At page 13, paragraph 19 of the Office Action, the Examiner rejects claims 1-2, 10 and 16 under 35 U.S.C. § 103(a) as being unpatentable over Dunlop *et al.* in view of Zhou *et al.*, or Hausser *et al.* or Cumberbatch *et al.* The Examiner states that Dunlop *et al.* teach a method of modulating the immune system by affecting the physiology of an antigen-presenting cell, and that the invention of claim 1 differs from the teaching of Dunlop *et al.* only in that the method comprises contacting said antigen-presenting cell with an effective amount of at least one retinoid and one cytokine. The Examiner also states that the invention of claim 10 differs from Dunlop *et al.* only in the method wherein the cytokine is TNFα or IL-1β. The Examiner states that Hausser *et al.* teach that treating monocyte-derived dendritic cells with TNF or soluble CD40L leads to enhanced MHC and accessory surface antigen expression with significantly elevated T cell stimulatory activity, and that Cumberbatch *et al.* teach that intradermal administration of TNFα or IL-1 activate epidermal Langerhans cells, characterized by the acquisition of a more dendritic morphology and the increased expression of Ia molecules. According to the Examiner, Cumberbatch *et al.* also teach that both IL-1β and TNFα can each stimulate the migration of epidermal Langerhans cells. The Examiner concludes that it would have been obvious to one of ordinary skill in the art to modulate the immune system as taught by Dunlop *et al.* by including cytokines as taught by Zhou *et al.*, Hausser *et al.* or Cumberbatch *et al.* The Examiner restates the purported teachings of the cited art as motivation to combine the art. Applicants respectfully disagree with these contentions and traverse the rejection.

Dunlop *et al.* and Zhou *et al.*, or Hausser *et al.*, or Cumberbatch *et al.*, provide no suggestion or motivation to one of ordinary skill to combine their disclosures, nor is there knowledge generally available to those of ordinary skill in the art that provides such motivation or suggestion. There is also no suggestion of a reasonable likelihood of success in making or using the claimed invention as a result of combining the cited references. The Examiner has taken selected portions of isolated disclosures and reconstructed them in an attempt to render the claimed invention obvious. This is impermissible hindsight reconstruction that fails to establish a *prima facie* case of obviousness.

In view of the foregoing remarks, Applicants respectfully request that the rejection under 35 U.S.C. § 103(a) over Dunlop *et al.* and Zhou *et al.*, or Hausser *et al.*, or Cumberbatch *et al.* be reconsidered and withdrawn.

D. Dunlop et al. and Zhou et al., or Hausser et al. or Cumberbatch et al. and further in view of U.S. Patent No. 5,552,271

At page 14, paragraph 20 of the Office Action, the Examiner rejects claims 4-5 under 35 U.S.C. § 103(a) as being unpatentable over Dunlop *et al.* in view of Zhou *et al.*, or Hausser *et al.* or Cumberbatch *et al.* as applied to claims 1-2, 10 and 16 and further in view of U.S. Patent No. 5,552,271 to Pfahl *et al.* According to the Examiner, claim 4 differs from the combined teachings of the references only in that the retinoid is a pan-RXR agonist and an RAR antagonist, and claim 5 differs only in that the pan-RXR agonist is SR11237. The Examiner states that it would have been obvious to one of ordinary skill in the art to substitute the retinoid as taught by Dunlop *et al.* for the various retinoids taught by the '271 patent in combination with

the various cytokines as taught by Zhou *et al.*, Hausser *et al.* or Cumberbatch *et al.* The Examiner restates the purported teachings of the cited art as motivation to combine the art. Applicants respectfully traverse the rejection.

For the reasons discussed above, there is no suggestion or motivation in the cited references that would have led one of ordinary skill to combine Dunlop *et al.* and Zhou *et al.*, or Hausser *et al.*, or Cumberbatch *et al.* or the '271 patent, and that would also suggest a reasonable likelihood of success in making or using the claimed invention as a result of that combination. The Examiner again uses impermissible hindsight reconstruction to combine unrelated pieces of art in an attempt to render the claimed invention obvious. Therefore, the Examiner has not met the burden required to sustain a *prima facie* case of obviousness.

In view of the foregoing remarks, Applicants respectfully request that the rejection under 35 U.S.C. § 103(a) over Dunlop *et al.* and Zhou *et al.*, or Hausser *et al.*, or Cumberbatch *et al.*, and further in view of the '271 patent be reconsidered and withdrawn.

E. Summary

Applicants submit that, upon careful analysis of the cited references, the skilled artisan would have found no motivation to combine or modify the reference teachings to arrive at a method of modulating the immune system within the scope of the present claims. Neither is there knowledge generally available to one of ordinary skill in the art that would provide the motivation or suggestion to combine the cited references. Finally, even if the cited references could be properly combined (which they cannot), Applicants respectfully assert that these combined disclosures would not

have rendered the claimed invention obvious. Accordingly, a *prima facie* case of obviousness has not been established, and reconsideration and withdrawal of the rejections under 35 U.S.C. §103(a) is respectfully requested.

Conclusion

All of the stated grounds of objection and rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider all presently outstanding objections and rejections and that they be withdrawn. Applicants believe that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of this Amendment and Reply is respectfully requested.

Respectfully submitted,

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Date: March 8, 2004

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